providing an identifying agent;

delivering the identifying agent through at least one breast duct;

allowing the delivered identifying agent to bind to premalignant or malignant cells within said lymph nodes and unbound portions of the delivered identifying agent to be eliminated from said at least one duct;

determining the lymph node involvement after said unbound portions of said delivered identifying agent have exited said at least one breast duct; and

identifying the location of said lymph node involvement.

REMARKS

The Office Action of March 11, 2002 has been received and considered. In the Office Action, claims 1-16 were rejected under 35 U.S.C. §112 and either 35 U.S.C. §102(b) or 35 U.S.C. §103(a).

Claims 1, 5, 9 and 13 have been amended to include certain suggestions set forth in the Office Action. Claims 17-32 have been deleted. Claims 1-16 remain pending. Reconsideration of the application is respectfully requested.

Claims 9-16 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification so as to enable one skilled in the art to which it pertains to make and/or use the invention. These claims have also been rejected under 35 U.S.C. §112, second paragraph. The Office Action asserts the following points: (1) the application does not define "lymph node involvement"; (2) the specification does not teach how the presence of an agent within a lymph node predicts lymph node involvement; (3) the specification does not disclose an example of how the present invention can be used to determine lymph node involvement; (4) the specification does not teach taking biopsies or performing

histopathologic examinations of the lymph nodes; and (5) practicing the method of the present invention would require undue experimentation.

Addressing point 1, the originally filed specification clearly defines "lymph node involvement" on page 6, lines 25-32. From a fair reading of this portion of the originally filed specification, it is clear that "lymph node involvement" includes when a tumor or lesion has spread to a sentinel lymph node. Additionally, applicants submit that the meaning of the phrase "lymph node involvement" is well within the knowledge of one of ordinary skill in the art. Therefore, contrary to the position taken in the Office Action, one of ordinary skill in the art would understand the meaning of the phrase "lymph node involvement" after reading the originally filed specification.

One of ordinary skill in the art would also understand when the lymph nodes were involved when practicing the present invention. Specifically, the involvement of the lymph nodes would be evident after the identifying agent or compound was introduced into the breast duct, allowed to bind to the precancerous or cancerous cells in the duct, including the lymph nodes, and then the unbound agent or compound eliminated from the duct. As discussed in the examples, the unbound agent could be eliminated from the duct by washing the duct with saline.[1] Hence, the originally filed specification teaches one of ordinary skill in the art that involved lymph nodes include those lymph nodes containing a bound identifying agent or compound after the duct has been washed. Also, since this is clearly taught, a working example specific to just lymph node involvement is not necessary.

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[1] Ductal washing can be performed by the methods discussed in a plurality of the patent applications incorporated by reference in the originally filed specification.

With regard to points (4) and (5) raised in the Office Action, the methods recited in claims 9-16 specifically eliminate the need for the invasively obtaining and removing steps of cells for histopathologic examination discussed in the outstanding rejection because it uses the natural, inherent functioning of the lymph nodes to determine the lymph node involvement. The natural function of the lymph nodes is to receive fluid from within the duct and allow it to pass into and through the node before draining into other parts of the body. Hence, when a sentinel lymph node has an associated lesion, the cancer specific agent will bind to it. For those nodes without an associated lesion, the agents will flow through them and not leave any indicator. Therefore, the location of the bound agent or compound can be identified after the introduced agent or compound has passed into the sentinel lymph nodes and the at least one duct, which includes its lymph nodes, has been washed to remove any unbound agent or compound. As a result, a need to invasively determine the lymph node involvement is not needed because only those nodes with a lesion will have a bound agent that is identifiable by non-invasive techniques. Similarly, undue experimentation is not needed because if the delivered agent or compound binds within a lymph node, then lymph node involvement has been detected when the identifying step is performed.

In formulating the rejections of claims 9-16, the Office Action misinterprets the remarks set forth in the previously filed response. The present invention does include a method for determining lymph node involvement by determining if the sentinel lymph nodes contain cancerous or precancerous cells or are receiving drainage from a lesion. In the previous remarks, applicants were merely clarifying that the prior art, unlike the present invention, "maps" and non-specifically identifies an entire ductal network and all of its lymph nodes. Instead, the present invention is directed to identifying those lymph nodes that include premalignant or

malignant cells or drainage from a lesion. As discussed on page 12, lines 15-24, the identifying agents or compounds identify lesions to the sentinel nodes and thus the method of the present invention is more accurate than conventional surgical methods. The present invention provides a more precise identification of lymph nodes most likely to drain a particular lesion than does the prior art. At page 12, lines 23 and 24, the specification expressly teaches that the method according to the present invention provides a level of tumor or lesion staging previously unobtainable without an invasive or surgical procedure.

For all of the above-discussed reasons, applicants submit that the methods recited in claims 9-16 are fully enabled by the present specification and definite.

Claims 1-16 have also been rejected for not including, what are asserted to be, one or more essential steps. These steps are listed in the Office Action. Applicants have amended claims 1, 5, 9 and 13 to include certain steps for clarity of the pending claims. Applicants do not submit that the steps added to these claims are essential. Instead, these steps have been recited to improve the clarity of the pending claims. Specifically, claims 1, 5, 9 and 13 have been amended to recite steps in which the introduced agent or compound has been allowed to bind to the premalignant or malignant cells and the unbound agent or compound has been eliminated from the duct, including the lymph nodes. These claims have also been amended to recite that the location of the premalignant cells, the malignant cells or the involved lymph nodes is determined after the binding of the agent or compound. Hence, it is submitted that the relationship between the introduction and binding of the agent or compound to the premalignant cells, the malignant cells or the involved lymph nodes is clearly recited in the pending claims. Also, the step of allowing any unbound agent or compound to be eliminated has also been clearly recited within the claims.

As previously discussed, "essential matter" is not merely those elements or steps that form a portion of the invention. Instead, "essential matter" is defined in M.P.E.P. §2172.01 as elements, steps or the like that are described by the applicant(s) in the specification as essential to practicing the invention. Therefore, in order for a step in the method to be considered essential matter, the applicant(s) must have disclosed in the specification or arguments that this step was "essential" to the practicing of the invention.

In the Office Action, it was asserted that the claims should also be amended to include a step of correlating the data obtained in the detecting step to the anatomy of the patient because this step is "essential" to the method. In support of this position, the Office Action identifies that this step is discussed in both of the exemplary methods set forth in the specification. However, such an amendment is not necessary. Page 8, lines 6-9, of the specification clearly recites that the location of the premalignant cells, the malignant cells and the involved lymph nodes can be identified by performing a MRI, PET or other known means. Additional support for alternative identification techniques is found on page 11. The specification does not recite that a correlation step that is separate from the locating step is essential to the invention. Therefore, contrary to the position taken in the Office Action, the steps set forth in the two examples contained within the specification are merely examples of how the location of the premalignant cells, the malignant cells or the involved lymph nodes can be determined. In view of the clear teachings set forth in the specification regarding the techniques that can be used to identify and locate bound compounds or agents, the steps set forth in the exemplary methods cannot fairly be considered "essential matter." MPEP §2172.01. Hence, amendments to the pending claims to include the asserted "correlating" step are not required to clearly and completely recite the methods according to the present invention in view of the instant specification and the prior art.

With regard to the statement that the applicants have not provided factual evidence to support the position that the steps recited in the Office Action are not essential, applicants note that the burden of making such a showing has not shifted to the applicants since a prima facie case has not been established as discussed above. For all of the above-discussed reasons, withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is requested.

Claims 5-8 were rejected under 35 U.S.C. §102(b) as being clearly anticipated Hou et al. (Hou) as evidenced by VanZee et al. (VanZee). Hou discloses a method of performing galactography before excision in patients with nipple discharge. During the galactography method discussed in Hou, a discharging breast duct is identified and a contrast material is introduced into this duct. Then, a mammogram is performed on the patient. When the mammogram indicates that a duct should be removed due the presence of premalignant or malignant cells, methylene blue is introduced into the breast duct via a catheter to identify the boundary of the duct containing the cell(s). The methylene blue stains the entire duct so that a surgeon can identify, locate and remove the entire duct.

In the Office Action, it is submitted that the phrase "cancer cell specific identifying agent" is not defined in the specification. As a result, the position was taken that anything which stains a duct and shows the topography of a duct is a "cancer cell specific identifying agent." Applicants submit that one of ordinary skill in the art clearly understands the phrase "cancer cell specific identifying agent" to mean an agent that binds only to cancerous cells and not healthy cells. The level of skill cannot be lowered to that of a conventional dictionary as done in the Office Action in order to shoehorn Hou into a rejection. As clearly understood by one of ordinary skill in the art, methylene blue is a not specific to cancer cells - it does not bind only to cancer cells. Therefore, methylene blue is not a cancer cell specific identifying agent as recited

in amended claim 5. Hence, the step of introducing the methylene blue into the duct does not anticipate the step of "providing a premalignant or malignant cancer cell specific identifying agent" as recited in claim 5.

Moreover, applicants' position that Hou does not disclose the recited agent is supported by the need for the arguments set forth on page 9 of the Office Action. The position taken in the Office Action that one or more of the recited agents are not cancer cell specific identifying agents is not supported by any evidence. The compounds and agents set forth in the specification include known cancer cell specific identifying agents - agents that only bind to premalignant or malignant cells. Therefore, claim 5 is clear, supported by the originally filed specification, does not lack written description and not anticipated by Hou. Moreover, the method of Hou does not disclose the step of allowing a delivered identifying agent to bind to premalignant or malignant cells within the at least one duct or ductal network and unbound portions of the delivered identifying agent to be eliminated from the at least one duct.

For all of the above-discussed reasons, withdrawal of the rejection is requested.

Claims 1-16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hou in view of Allan et al. (Allan) and Vitetta et al. (Vitetta) as evidenced by Krag et al. As discussed above, Hou discloses a method of performing galactography on a patient. In the Hou method, the contrast material is introduced into the duct before the mammogram is performed. If the mammogram identifies that a surgical excision of a duct is necessary, methylene blue is introduced into the breast duct in question. After the introduction of the methylene blue, a precise surgical excision of the dye-stained ducts and lobules is performed. The methylene blue only maps the duct to be removed by the invasive surgical procedure. The methylene blue is not a targeting molecule coupled to an identifying agent that identifies the cancerous cells.

Similarly, the methylene blue is not a cancer cell specific identifying agent. Instead, it is only a dye that identifies the shape and boundary of the duct to be removed.

Allan discloses a method of radioimmunolocalization of a breast duct to facilitate surgical excision of tissue including and surrounding malignant breast cancer cells. The Office Action suggests that it would have been obvious to modify the method of Hou with the step of introducing the agent of Allan into the breast duct through a ductal opening. However, as discussed below, a prima facie case of obviousness has not been set forth because (1) no motivation exists for the asserted combination, (2) impermissible hindsight has been used to pick and choose portions of the Allan method while ignoring others, (3) no expectation of success exists for this modification and (4) the steps needed to prepare the agent disclosed in Allan's method contradict the method set forth in Hou.

It appears that Hou is being relied upon to teach the concept of intraductal introduction of a material. Allan discloses a method for developing an antibody that is systemically introduced into the body. In order to perform the method disclosed in Allan, the patient is first subjected to a mammogram. Then, if the mammogram identifies questionable cells, fine needle aspiration (FNA) or a core biopsy is performed on the tumor in the breast. As is well known in the art, FNA is a very uncomfortable procedure for the patient and can lead to the spreading of cancerous cells within the body. After the FNA or biopsy has been performed, the collected samples are analyzed. An antibody based on the fine needle aspirate is then developed. The developed antibody is then systemically introduced into the body.

Contrary to the position taken in the Office Action, the prior art does not provide motivation for the asserted combination. Instead, the only motivation for the asserted combination is that disclosed in the specification of the instant application. For example, the

motivation set forth in the outstanding Office Action is almost verbatim what applicants have disclosed as the benefits of the present invention. Allan and the systemic introduction of its antibody does not teach any of the benefits or the motivation discussed in the Office Action. Additionally, these benefits were not known to one of ordinary skill in the art because no one had introduced the recited agent or compound through a ductal opening prior to the invention of the applicants. Therefore, the general state of the prior art could not have provided the asserted motivation. Since no motivation exists in the prior art and the only suggestion is that provided by the applicants, the rejection is necessarily based on impermissible hindsight and the rejection must be withdrawn. See In re Vaeck, 974 F.2d 488 (Fed. Cir. 1991).

The Office Action suggests that motivation can be found in the increased specificity provided by the antibody developed using the Allan method. However, Allan only teaches introducing the developed antibody systemically and obtaining the specificity through systemic introduction. Allan's step of systemically introducing the antibody cannot be ignored. Allan has to be taken as a whole. Without some teaching in the prior art for introducing the antibody through a breast duct opening, no motivation exists for introducing the antibody into the patient anyway but systemically. Therefore, at best, one of ordinary skill in the art may have been motivated to modify the method of Hou to include a step of systemically introducing the antibody of Allan, but not introducing intraductally as recited.[2] Again, Allan's teaching of systemically introducing the agent cannot be ignored and cast aside as has been done in the formulation of the outstanding rejection because the prior art does not provide any expectation of success for the intraductal introduction of the antibody instead of the systemic introduction.

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[2] As discussed below, the applied references are not combinable even to arrive at the systemic introduction of Allan's antibody.

Absent some teaching in the prior art and expectation of success, the rejection cannot be sustained. See In re Vaeck, 974 F.2d 488 (Fed. Cir. 1991).

Moreover, modifying the method of Hou to include an agent that is intended to be eliminated from a duct would destroy the method of Hou. The methylene blue used in the method of Hou identifies the exact portion of the body that needs to be removed by the surgeon - the duct. Providing Hou with an agent that is intended to be eliminated from the duct and lymph nodes without any regard for staining the exact boundary of the duct to be removed would be contrary to the teachings of Hou and prevent its method from being performed as intended. The method disclosed in Hou could no longer be practiced. Therefore, one of ordinary skill would not have been motivated to make the asserted combination.

In the outstanding Office Action, it is asserted that applicants have not provided any evidence to support their "no expectation of success" arguments. No evidence is required because the burden is still upon the USPTO to establish a prima facie case of obviousness. At this time, a prima facie case of obviousness has not been set forth for the reasons discussed above. Therefore, until a prima facie case of obviousness has been set forth, the burden is not on the applicants to provide the evidence mentioned in the Office Action.

The rejection is also not sustainable for the following reasons. The method of Hou requires the mammogram to be performed after the identifying agent - contrast material - has been introduced into the breast duct. To the contrary, the steps of the Allan method require that the mammogram be performed before the agent, to be used in the Hou mammogram, is developed so that the tumor accessed during the FNA step can be located. The modification suggested in the Office Action would require that the steps of the Hou method be modified so that the mammogram of Hou is performed before the agent used in the Hou mammogram is

prepared and introduced into the body. The mammogram of Hou cannot be performed without its identifying agent - its contrast material. Additionally, no need exists for performing multiple mammograms. The asserted modification contradicts the teachings of Hou and would render its method inoperable. Therefore, such a modification would not have been obvious to one of ordinary skill in the art.

In the Office Action, it is asserted that the teachings of the Hou and Allan methods are "**immaterial**" when determining obviousness. Such a position flies in the face of a long line of well-settled case law. A reference must be considered for all that it teaches. It is clearly improper to pick and choose parts of a reference while ignoring others. In the instant application, the contradictory teachings of Hou and Allan have clearly been ignored. Hence, the rejection is improper and must be withdrawn because these contradictory teachings would not have motivated one of skill in the art to modify Hou to arrive at the claimed methods.

Like the disclosures of Hou and Allan, the disclosure of Vitetta et al. (Vitetta) does not teach introducing a targeting molecule coupled to an identifying agent or a cancer specific identifying agent into a breast through a breast duct. Therefore, like Allan, Vitetta would not have motivated one of ordinary skill to modify the method of Hou to arrive at the methods recited in claims 1-16. For all of the above-discussed reasons, withdrawal of the rejection is requested.

Claims 1-16 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,168,779 to Barsky et al. (Barsky) in view of Allan. as evidenced by Krag et al. and the internet contents of "oncologychannel.com."[3]

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[3] The oncologychannel.com document is not prior art and cannot be used in this rejection. The reference was downloaded in March of 2001. This date is one year and five months after the date that the instant application was filed. Therefore, this document is not prior art to the present application.

Barsky is directed to and discloses a method of identifying ductal orifices on a nipple surface. While Barsky does include a statement that diagnostic, therapeutic or other materials could be instilled into the duct, Barsky does not disclose or contemplate a method of identifying the location of premalignant or malignant breast cancer within a breast duct or ductal network as recited in claims 1-16. Hence it cannot disclose such a method that includes the step of delivering either a targeting molecule coupled to an identifying agent or a cancer specific identifying agent into a breast through a breast duct.

The disclosures relied upon in the Office Action on columns 3 and 4 of the Barsky patent relate to the location and identification of ductal openings. These disclosures do not and cannot be fairly considered to disclose steps for determining if the epithelial lining of the duct includes premalignant or malignant cells. These disclosures are limited to their specific teaching of ductal opening identification. The very broad interpretation of these statements set forth in the Office Action cannot be sustained when the patent is taken as a whole.

As discussed above, Allan discloses a method for systemically introducing an antibody into a patient for locating cancerous cells within the body. Allan does not disclose that the antibody can be introduced into the patient other than systemically. Neither reference provides any teaching of providing the recited targeting molecule and identifying agent or cancer specific agent into the breast by intraductal introduction. Therefore, Allan would not have motivated one of ordinary skill in the art to modify the method of detecting ductal orifices on the nipple surface with a method of systemically introducing an antibody into a patient to detect the presence of cancerous cells. No teaching exists in either Barsky or Allan that would have lead one of ordinary skill to modify the method of Barsky to arrive at the method recited in claims 1-

16. Additionally, there is no expectation of success for the asserted combination. Withdrawal of the rejection is requested.

In the Office Action, it is asserted that the asserted combination would have been obvious because "it does not take much **imagination** to visualize a method such as that of the present claims." However, "imagination" is not the test for obviousness under 35 U.S.C. §103(a). Instead, the test under 35 U.S.C. §103(a) requires the existence of a teaching and motivation in the prior art to combine the asserted references to arrive at the claimed invention. It is well settled that the prior art, not applicants' disclosure, must provide the teaching and motivation for the asserted combination. See In re Vaeck, 947 F.2d 488. The prior art fails to provide this required teaching. Again, as discussed above with respect to the rejection based on Hou, the only motivation for the asserted combination is that disclosed by the applicants. Therefore, the rejection must be withdrawn.

As discussed in the above-noted footnote, the Oncologychannel.com publication cannot be used as a teaching of the state of the art at the time the invention was made because it was downloaded almost 1.5 years after the application was filed. This publication does not satisfy any of the statutory requirements under 35 U.S.C. to qualify as prior art to the present application. Hence, any rejection relying on this reference cannot be maintained. The Office Action suggests that applicants somehow agree with the contents of the Oncologychannel.com publication because they do not argue its alleged teachings. This argument is groundless. When the USPTO has not satisfied its burden of establishing a prima facie case of obviousness and the publication cited does not qualify as prior art, it is not the applicants' burden to argue the scope and content of the publications - it is not prior art to the pending application. Instead, it is only applicants' burden to point out the error on the part of the USPTO - which is what has been done

in the instant application. Withdrawal of the rejection and the reliance on the Oncologychannel.com publication is requested.

For all of the above-discussed reasons, Applicants respectfully submit that claims 1-16 are allowable and that the application is now in condition for allowance. A notice to this effect is earnestly solicited.

It is requested that the amendments to claims 1-16 be entered for, as discussed above, they place the application in condition for allowance. Alternatively, these amendments should be entered for they place the application in better condition for appeal and do not raise any new issues. Instead, the amendments merely incorporate claim modifications suggested in the outstanding Office Action. Entry of the above listed amendments is requested.

If any questions or issues remain, the resolution of which the Examiner feels would be advanced by a conference with Applicants' attorney, the Examiner is invited to contact Applicants' attorney at the number noted below.

Respectfully submitted,

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Marked-Up Version of Amended Claims for 09/410,336

Please amend claims 1, 5, 9 and 13 to read as follows.

1. (Twice Amended) A method of identifying the location of premalignant or malignant [breast cancer] cells within a breast duct or breast ductal network, said method comprising:

providing a compound comprising a targeting molecule coupled to an identifying agent;

delivering the [coupled] compound through at least one breast duct [in an amount sufficient to identify premalignant or malignant cancerous cells];

allowing the delivered compound to bind to premalignant or malignant cells within said at least one duct or ductal network and unbound portions of the delivered compound to be eliminated from said at least one duct; and

identifying the location of the premalignant or malignant [cancer] cells bound to said compound within the at least one breast duct or ductal network [after the coupled compound has been delivered within the at least one duct].

5. (Twice Amended) A method of identifying the location of premalignant or malignant [breast cancer] cells within a breast duct or breast ductal network, said method comprising:

providing a premalignant or malignant cancer cell specific identifying agent;

delivering the identifying agent through at least one breast duct [in an amount sufficient to identify premalignant or malignant cancerous cells];

allowing the delivered identifying agent to bind to premalignant or malignant cells within said at least one duct or ductal network and unbound portions of the delivered identifying agent to be eliminated from said at least one duct; and

identifying the location of the premalignant or malignant [cancerous] cells bound to said identifying agent within the at least one breast duct or ductal network [after the coupled compound has been delivered within the at least one duct].

9. (Twice Amended) A method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths, said method comprising:

providing a compound comprising an identifying agent coupled to a targeting agent;

delivering the [coupled] compound through at least one breast duct [in an amount sufficient to detect lymph node involvement];

allowing the delivered compound to bind to premalignant or malignant cells within said lymph nodes and unbound portions of the delivered compound to be eliminated from said at least one duct;

determining the lymph node involvement after said [coupled compound has been delivered in] unbound portions of the delivered compound have exited said at least one breast duct; and

identifying the location of said lymph node involvement.

13. (Twice Amended) A method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths, said method comprising:

providing an identifying agent;

delivering the identifying agent through at least one breast duct [in an amount sufficient to detect lymph node involvement];

allowing the delivered identifying agent to bind to premalignant or malignant cells within said lymph nodes and unbound portions of the delivered identifying agent to be eliminated from said at least one duct;

determining the lymph node involvement after said unbound portions of said delivered identifying agent have exited [coupled compound has been delivered in] said at least one breast duct; and

identifying the location of said lymph node involvement.